Heliyon 9 (2023) e18504

Contents lists available at ScienceDirect

Heliyon

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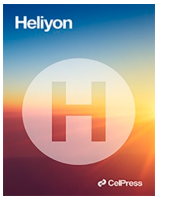

Review article

Targeting ferroptosis in renal cell carcinoma: Potential mechanisms and novel therapeutics

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ARTICLE INFO

Keywords:
Renal cell carcinoma
Ferroptosis
Progression
Treatment
Prognosis

ABSTRACT

Renal cell carcinoma (RCC) is an increasingly prevalent urologic malignancy that impacts human health worldwide. Surgery is an effective strategy for early RCC treatment, but advanced RCC is resistant to chemotherapy, thus development of other potential therapeutic strategies is urgent. Ferroptosis is a newly defined form of programmed cell death characterized by accumulation of iron-dependent lipid peroxides and plays a crucial role in the tumor progression and drug resistance. Recent studies have shown that ferroptosis participates in RCC progression and chemoresistance. Therefore, identifying the potential role of ferroptosis in RCC could develop novel therapeutic targets and clinical markers for this disease. This review concisely summarizes the regulatory role of iron, amino acid, and lipid metabolism in ferroptosis, as well as discusses the relationship between ferroptosis and RCC, and details the role of ferroptosis in tumor progression, which indicates that various ferroptosis regulators are dysregulated in RCC and exert paradoxical effects, either tumor-suppressive or oncogenic. These ferroptosis-related regulators are expected to be used as clinical markers for RCC prognosis. Thus, targeting these regulators to trigger ferroptosis may be the key to the development of potential therapeutic strategies for this disease.

1. Introduction

Renal cell carcinoma (RCC) is one of the most common urologic cancers with high morbidity and high-grade malignancy, accounting for 85% of malignant renal tumors [1]. RCC is classified into three distinct histological subtypes, including clear cell RCC, papillary RCC, and chromophobe RCC [2]. Partial and radical nephrectomy are the mainstreams for early RCC treatment, which contribute to a positive prognosis with a 5-year survival rate of approximately 93% [3]. However, it is estimated that 20–30% of patients who have received a successful nephrectomy experience a recurrence and even distant metastasis to lung, bone, liver, and brain, which is largely responsible for RCC-associated deaths [4]. Although immunotherapy benefits patients with advanced RCC, but drug resistance occurred in these patients results in unfavorable prognosis [5]. Therefore, it is imperative to develop novel approaches for RCC treatment.

Ferroptosis is an emerging form of programmed cell death that is gradually regarded as an adaptive process to eradicate cancer cells that resistant to other types of programmed cell death, such as apoptosis and autophagy [6]. Thus, activation of ferroptosis is considered to be an ideal therapeutic strategy of cancer and may help to overcome drug resistance [7]. The initiation of ferroptosis is

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https://doi.org/10.1016/j.heliyon.2023.e18504
Received 16 March 2023; Received in revised form 15 July 2023; Accepted 19 July 2023
Available online 21 July 2023

mainly involved in iron accumulation, amino acid, and lipid metabolism (Fig. 1). Increasing studies have been implicated the contribution of ferroptosis in the pathogenesis of RCC, and indicated that some agents can induce ferroptosis in RCC cells [8–10]. These findings provide the possibility that using inducers of ferroptosis or regulating ferroptosis-related genes become a novel strategy for RCC treatment. Therefore, understanding the role of ferroptosis in RCC is great significance. This review summarizes the relationship between ferroptosis and RCC and roles of ferroptosis in RCC progression, treatment, and prognosis, as well as discusses the potential application of ferroptosis in RCC therapies.

2. Review criteria

In order to summarize the role of ferroptosis in RCC, a PubMed search was performed in March 2023. Articles containing the following key words were considered for inclusion: “renal cell carcinoma” AND “Ferroptosis”. The research strategy is: (Carcinoma, Renal Cell [Mesh] OR renal cell carcinoma [title/abstract]) AND (Ferroptosis [Mesh] OR Ferroptosis [title/abstract]). Relevant research articles were also identified from a manual search of reference lists within those included. The abstracts of identified research articles were screened and classified for inclusion in the review. To be included, the article must have described original data concerning the relationship between ferroptosis and RCC, and have been published in a peer-reviewed journal and written in English. The PRISMA flow chart of this study is illustrated in Fig. 2.

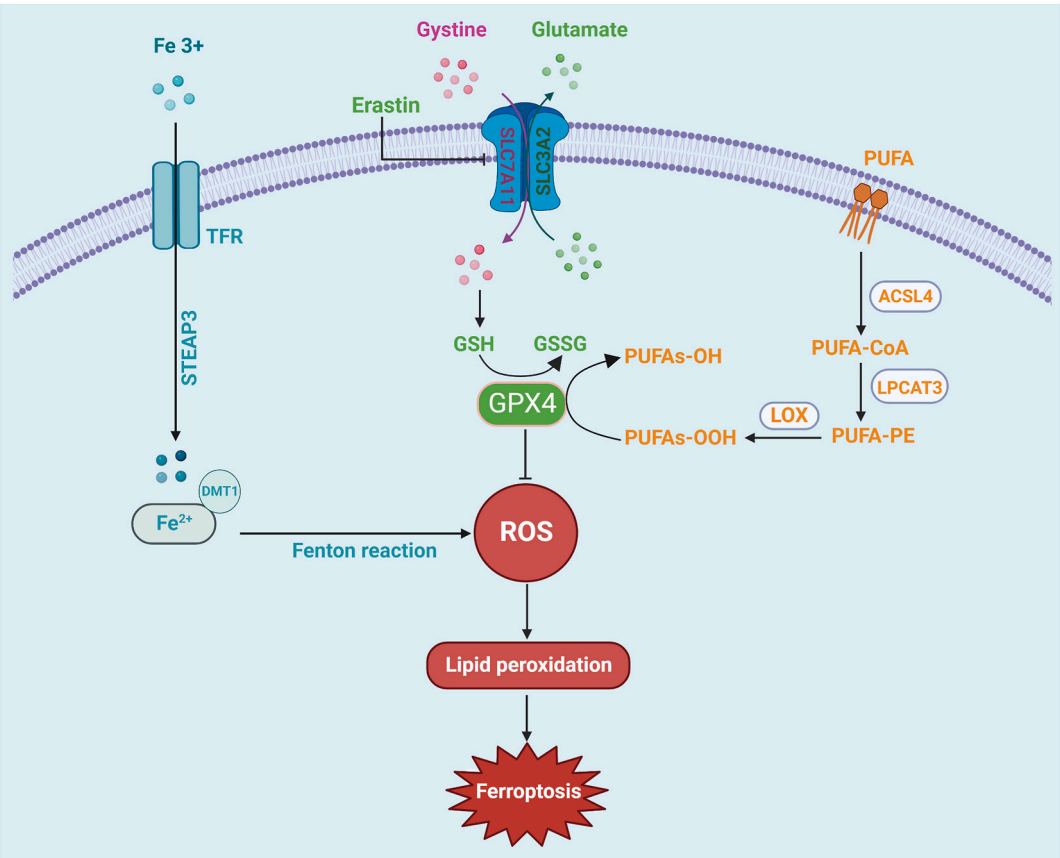

Fig. 1. The main mechanisms of ferroptosis in RCC. Extracellular Fe^{3+} combined with transferrin are endocytosed into cell via TFR. STEAP3 converts Fe^{3+} into Fe^{2+}, and Fe^{2+} is released from DMT1 to the unstable iron pool in the cytoplasm to mediate lipid ROS and ferroptosis. The SLC7A11/SLC3A2 transporter exports intracellular glutamate and imports extracellular cystine, which is then converted to cysteine for GSH synthesis. Erastin can inhibit the activity of SLC7A11. GPX4 can inhibit the accumulation of ROS with the help of GSH. Amino acid metabolism dysfunction can inhibit intracellular GSH and GPX4 to prompt ferroptosis. Under the action of ACSL4 and LPCAT3, PUFA synthesizes PUFA-PE, which are oxidized to PUFA-OOH by LOX, and GPX4 converts the toxic PUFA-OOH to nontoxic PUFA-OH, thereby inhibiting the occurrence of ferroptosis. ROS: reactive oxygen species; SLC7A11: solute carrier family 7 member 11; SLC3A2: solute carrier family 3 member 2; GSH: glutathione; GPX4: glutathione peroxidase 4; TFR: transferrin receptor; STEAP3: iron oxide reductase steam 3; DMT1: divalent metal transporter 1; PUFA: polyunsaturated fatty acid; ACSL4: acyl-CoA synthetase long-chain family member 4; LPCAT3: lysophosphatidylcholine acyltransferase 3; LOX: lipoxygenases. → indicates a promoting effect and ⊥ indicates an inhibitory effect.

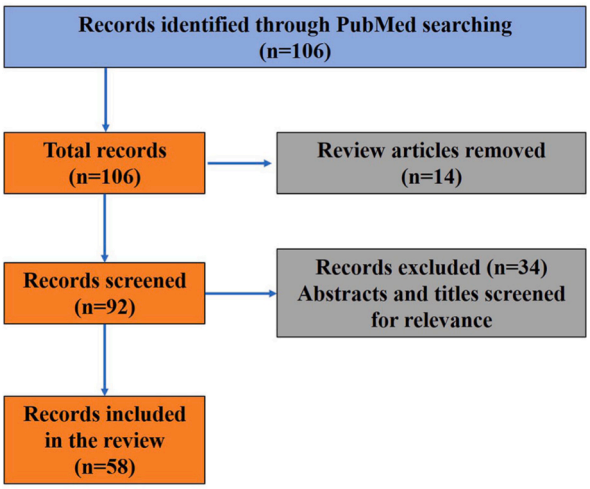

Fig. 2. PRISMA flow chart.

3. Main mechanisms of ferroptosis

3.1. Iron metabolism

Iron metabolism is an essential cellular process for the occurrence of ferroptosis, and iron overload causes ferroptosis in cancer [11]. Iron generally exists in two different forms including ferric cation (Fe^{3+}) and ferrous cation (Fe^{2+}). Serum free Fe^{3+} binds to transferrin proteins, and these iron–protein complexes interact with transferrin receptor 1 (TFR1), a transmembrane glycoprotein expressed on the cell membrane, and subsequently enter the cell through endocytosis [12]. Iron oxide reductase steam3 (STEAP3) mediates the conversion of the form of Fe^{3+} into the form of Fe^{2+} [13]. Excessive iron can be also reserved as ferritin, and the ferritin heavy chain has iron oxidase activity that is responsible for the conversion of Fe^{2+} into Fe^{3+}, allowing iron to be safely incorporated into the ferritin shell and thus lowering free iron levels [14]. Fe^{2+} is transported into the cell through the divalent metal transporter 1 (DMT1)-mediated endosome and is further released into cytoplasmic iron pool [15]. Thus, the intracellular iron storage is presented by two states, either ferritin or free Fe^{2+} in iron pools. Under normal conditions, cellular iron concentrations remain stable. However, in cases of iron overload, Fe^{2+} is overproduced and reacts with hydrogen peroxide via the Fenton chemical reaction to produce hydroxyl radicals with potent oxidant properties, which subsequently generates large amounts of lipid peroxides [16]. Besides, iron augments ROS generation by activating ROS-generating enzymes, such as nicotinamide adenine dinucleotide phosphate oxidases and lipoxygenases [17]. Excessive ROS accumulation and lipid peroxidation lead to cell membrane damage and lipid peroxidation, ultimately resulting in ferroptosis. As a major organelle for cellular ROS generation, mitochondria produce lipid ROS upon cysteine deprivation, thus regulating the process of ferroptosis [18]. By using mitochondrial ROS quenchers, ferroptosis is inhibited, which is accompanied by abrogation of ferroptosis inducers-mediated mitochondrial ROS and oxidized lipid accumulation [19]. These findings suggest a critical role of mitochondrial ROS in ferroptosis.

It should be noted that RCC tumor tissues have higher iron levels compared to solid tumors of other organs, such as liver, prostate, and stomach; moreover, iron levels in RCC cells are reduced with the tumor development, including pathologic staging, sarcomatous dedifferentiation, and distant metastasis [20]. Therefore, the modulation of iron metabolism and resultant ferroptosis may be a promising factor in limiting RCC progression. Moreover, at the early stage of renal tumorigenesis, iron overload can produce hydroxyl radicals via Fenton reaction to trigger ferroptosis in renal proximal tubules, thus causing oxidative renal damage; however, once a neoplasm has formed, iron and its metabolites evoke tumor suppressors to resist ferroptosis, which favors RCC progression [21]. In this regard, future experimental settings should take the iron concentrations that induce ferroptosis, and the different stages of RCC into consideration.

3.2. Amino acid metabolism

Amino acid metabolism participates in the regulation of ferroptosis, mainly by regulating system Xc^-, glutathione (GSH), and GPX4. System Xc^-, also named cystine (Cys)/glutamate (Glu) antiporter, containing a catalytic subunit solute carrier family 7 member 11 (SLC7A11) and a regulatory subunit solute carrier family 3 member 2 (SLC3A2) that linked together through a disulfide bridge, uptakes extracellular Cys but releases intracellular Glu in a 1:1 ratio, and the smuggled Cys is induced to cysteine that is used for the synthesis of GSH, which serves as an antioxidant that is utilized in enzymatic and non-enzymatic antioxidant reactions to maintain the redox balance [22,23]. In coordination with cofactor GSH, GPX4 consumes lipid peroxides and neutralizes ROS, thus defying oxidative stress [24]. Dysfunction of amino acid metabolism attributed to both suppression of system Xc^- and deficiency of GSH or GPX4, can trigger ferroptosis. Indeed, erastin, a small-molecule inhibitor targeting system Xc^-, represses cysteine intake and GSH production,

thereby contributing to lipid ROS accumulation and subsequent ferroptosis [25]. Another ferroptosis inducer RSL3, interacts with GPX4 and inactivates its phospholipid peroxidase activity, which induces the accumulation of lipid peroxides and further ferroptosis [26].

In RCC, SLC7A11 is upregulated to facilitate the proliferation, migration, and invasion of cancer cells by elevating GPX4 expression, which in turn impairs ferroptosis [27]. Thus, targeting GPX4 may act as a therapeutic potential in RCC [28]. Of importance, diverse pathological types of RCC differ in sensitivity to disruption of amino acid metabolism. Clear cell RCC are highly susceptible to the depletion of Glu or Cys, and loss of GSH in these cells fails to eliminate cellular hydroperoxides and thus reduces cell viability [29]. Compared with clear cell RCC, chromophobe RCC has higher levels of GSH and lower expression of γ-glutamyl transferase 1, an enzyme in GSH homeostasis, thereby presenting higher sensitivity to ferroptosis induction [30]. Identifying the roles of ferroptosis in the amino acid metabolic vulnerability of distinct RCC tumors offers a promising avenue for targeted therapy. In addition, deprivation of Cys in VHL-deficient cell lines and primary clear cell RCC cells initiates rapid programmed necrosis, and blocking Cys uptake delays xenograft growth of RCC [31]. This result indicates that ferroptosis-regulating amino acid metabolic pathways are also involved in the induction of other programmed cell death processes. Elaborating the intrinsic crosstalk between ferroptosis and these processes is crucial for understanding the pathogenesis of RCC. Emerging ferroptosis-related genes have been demonstrated to participate in amino acid metabolism in RCC. For example, the decreased ACADSB expression might promote RCC tumorigenesis and progression by inhibiting branched-chain amino acid catabolism and further downregulating the expression of ferroptosis driver genes [32,33]. However, the regulatory mechanism of ferroptosis-related genes on amino acid metabolism and downstream signaling pathways are still vague. Further clarifying the roles of ferroptosis-regulating amino acid metabolic pathways in the pathogenesis of RCC might provide potential therapeutic targets to tackle this disease.

3.3. Lipid metabolism

Lipid peroxidation causes oxidative damage to the cell membrane and ultimately leads to ferroptosis. Among components of cell membranes, polyunsaturated fatty acids (PUFAs), including phosphatidylethanolamines (PEs) containing arachidonic acid (AA) or its derivative adrenergic acid (AdA), are more predisposed to oxidation by various ROS such as hydroxyl radical and hydrogen peroxide, and subsequently generate lipid peroxides, triggering ferroptosis by inducing rupture of phospholipid structures in biofilms [34]. During lipid peroxidation, several enzymes, including acyl-CoA synthetase long-chain family member 4 (ACSL4), lysophosphatidylcholine acyltransferase 3 (LPCAT3), and lipoxygenases (LOX), are involved in lipid metabolism and function as positive regulators of ferroptosis. Upon activation of ACSL4, AA is acylated to form AA-CoA, which is further converted to AA-PE by LPCAT3. This process facilitates the esterification and incorporation of PUFAs into membrane phospholipids, sensitizing cells to ferroptosis [35,36]. Meanwhile, LOX oxidizes AA-CoA and thus produce AA-OOH-CoA [37]. In this context, suppression of ACSL4, LPCAT3, or LOX inhibits ferroptosis [38,39]. However, the acyl-CoA synthetase long-chain family member 3 (ACSL3), induces exogenous monounsaturated fatty acids to replace PUFAs in cell membranes, hindering lipid ROS accumulation and membrane oxidation, and thus impeding

Table 1
Promising molecules of renal cell carcinoma targeting ferroptosis.

Molecule	Expression	Regulatory mechanism on ferroptosis	Function	Study types	Ref.
ACSL3	Normal	Renders RCC cell sensitive to erastin-induced ferroptosis by promoting lipid production	Tumor-suppressor	In vitro, in vivo	[47]
SDH	Down	Its suppression reduces ferroptosis by compromising oxidative phosphorylation	Tumor-suppressor	Human tissue, in vitro	[48]
KDM5C	Down	Its depletion confers RCC cell resistance to ferroptosis by increasing glycogen	Tumor-suppressor	In vitro, in vivo	[49]
KLF2	Down	Induces ferroptosis by triggering the transcriptional inhibition of GPX4	Tumor-suppressor	Human tissue, In vitro, in vivo	[8]
TAZ	Up	Its overexpression sensitizes RCC cell to ferroptosis through the EMP1/NOX4 axis	Tumor-suppressor	In vitro, in vivo	[50]
MT1G	Down	Abrogates erastin and sorafenib-induced ferroptosis by regulating GSH consumption	Oncogene	Human tissue, in vitro	[51]
Lcn-2	Up	Protects RCC cell from erastin-induced ferroptosis by activating the Nrf2 and eIF-2α/ATF4 pathway	Oncogene	In vitro	[52]
Adipokine chemerin	Up	Blocks ferroptosis by activating HIF-2α	Oncogene	Human tissue, In vitro, in vivo	[53]
ISCA2	Down	Its repression increases ferroptosis by suppressing HIF-1/2α	Oncogene	In vitro, in vivo	[54]
MITD1	Up	Its knockdown promotes ferroptosis through the TAZ/SLC7A11 pathway	Oncogene	In vitro, in vivo	[55]
STEAP3	Up	Its silencing promotes erastin-induced ferroptosis by activating the p53/xCT pathway	Oncogene	Human tissue, in vitro	[13]
SUV39H1	Up	Its deficiency facilitates ferroptosis by upregulating the DPP4	Oncogene	Human tissue, In vitro, in vivo	[56]
miR-4735-3p	Down	Its mimic accelerates ferroptosis by inactivating SLC40A1	Tumor-suppressor	Human tissue, in vitro	[57]
lncRNA SLC16A1-AS1	Up	Its knockdown induces ferroptosis through the miR-143-3p/SLC7A11 axis	Oncogene	In vitro, in vivo	[58]

ferroptosis [40], indicating a negative regulatory effect of ACSL3 on ferroptosis. When ferroptosis occurs, lipid peroxidation metabolites derived from PUFAs, such as 4-hydroxy-2-nonenal and malondialdehyde (MDA), impair lipids, proteins, and nucleic acids, aggravating ferroptosis-mediated cell death [41].

In clear cell RCC tissues, which accumulate a large amount of PUFAs, abnormal lipid metabolism facilitates tumorigenesis [42]. Targeting PUFAs via a nanodrug to generate lipid peroxides has become a potential strategy to induce ferroptosis for RCC treatments [43]. Furthermore, the expression level of ACSL4 is decreased in clear cell RCC cells, which is associated with advanced tumor progression and short overall survival, suggesting that ACSL4 represents a novel promising therapeutic target for RCC [44]. In addition, the natural agent lycorine exerts the anti-tumor effect in RCC through inducing ferroptosis by elevating ACSL4 and MDA expression [45]. Thus, it is vital to identify the regulators that mediate the lipid peroxidation in RCC. Moreover, lipid oxidation suppression and fatty acid metabolism dysfunction make RCC highly dependent on the GSH/GPX pathway to prevent lipid peroxidation and cell ferroptotic death [46]. Hence, targeting lipid metabolic pathways to trigger ferroptosis has become a promising therapy for RCC.

3.4. Roles of ferroptosis in RCC progression

Ferroptosis and ferroptosis-related regulators have been widely investigated. Generally, some regulators can be employed as tumor suppressors to inhibit the occurrence and development of RCC, while others exert an oncogenic effect (Table 1).

3.5. The tumor-suppressive effect of ferroptosis

The proliferation, migration, and invasion of cancer cells are crucial events in the progression of malignancies. Ferroptosis has been implicated in RCC progression. Emerging studies have found that ferroptosis-regulated genes and proteins have an impact on the development of RCC. The enzyme acyl-CoA synthetase 3 (ACSL3), converting exogenous fatty acids into lipid droplets, enhances the sensitivity of RCC cells to ferroptosis depending on the composition of exogenous fatty acids, indicating an underlying therapeutic target for RCC [47]. It is reported that the succinate dehydrogenase (SDH) is downregulated in RCC tissues and participates in tumor progression, with reduced ROS levels, peroxide accumulation, and ferroptosis, suggesting a tumor-suppressing role of SDH in RCC [48]. The ferroptosis-related gene KDM5C is identified in RCC, and in vivo and in vitro experiments find that silencing of this gene induces cells resistance to ferroptosis by upregulating GSH, while restoring its expression inhibits the glucose accumulation, and accelerates lipid peroxidation and ferroptosis in RCC cells [49]. Lu et al. demonstrated that kruppel-like factor 2 (KLF2), which is expressed at a low level in primary metastatic RCC and indicates unfavorable prognosis in patients, suppresses cell growth, migration, and invasion by inducing the transcriptional repression of GPX4 and thus mediating ferroptosis in RCC [8]. Besides, TAZ, a transcriptional co-activator with PDZ-binding motif, is confirmed to sensitize RCC cells to ferroptosis and further limits tumor growth, invasion, and metastasis through activating the EMP1/NOX4 signaling pathway, leading to ROS generation [50]. These findings imply that positive regulators of ferroptosis inhibit RCC development and may be employed as a therapeutic strategy for RCC.

In conclusion, some ferroptosis-related regulators are expressed differently in RCC and exert an inhibitory effect acting as tumor suppressors, which facilitate ROS accumulation, lipid peroxidation and thus ferroptosis. It is generally acknowledged that ferroptosis-related tumor suppressors are downregulated in most cases owing to their roles as ferroptosis inducers. However, several regulators are upregulated in tumor tissues and sensitize RCC cells to ferroptosis. The exact mechanisms of this phenomenon are still elusive. One explanation may be that upregulated regulators act as intermediate factors to modulate downstream signaling pathways and further to affect ferroptosis. Therefore, rejuvenation of these low expressed regulators in RCC patients may offer a potential therapeutic strategy by inducing ferroptosis. Furthermore, some tumor suppressors link ferroptosis to the tumor microenvironment and have been implicated in RCC development. For instance, CX3CL1 is related to the infiltration level of $CD8^+$ T cells, and overexpression of CX3CL1 suppresses RCC proliferation and metastasis by promoting the sensitivity of ferroptosis in tumors [59]. Also, in the von Hippel Lindau (VHL) mutant RCC, the LCN-2 is activated to trigger ferroptosis, accompanied by enhanced ROS production and reduced GPX4 expression, as well as sensitizes RCC cells to inflammation and macrophages to M1-like polarization, thus restricting the progression of RCC [60]. Given the critical role of VHL mutation and ferroptosis in RCC, further studies are required to investigate whether ferroptosis is regulated by VHL status in RCC.

3.6. The oncogenic effect of ferroptosis

Several negative regulators of ferroptosis are verified to promote RCC progression. For example, metallothionein 1 G (MT1G) is reduced in clear cell RCC tissues and is associated with poor survival, and in vitro experiments show that MT1G blocks both erastin and sorafenib-induced ferroptosis in RCC cells by regulating GSH consumption [51]. Research also demonstrated that iron-bound lipocalin-2 (Lcn-2) prevents RCC cells against erastin-induced ferroptosis through activating of the antioxidant Nrf2 pathway and the eIF-2α/ATF4 pathway [52]. Additionally, adipokine chemerin is overexpressed to inhibit fatty acid oxidation in clear cell RCC cells, which blocks ferroptosis by stimulating HIF-2α, contributing to RCC progression [53]. Thus, targeting negative regulators of ferroptosis impedes the development of RCC. Green et al. found that iron sulfur cluster assembly 2 (ISCA2) levels are decreased in clear cell RCC, which is related to the loss of VHL tumor suppressor protein; also, repression of ISCA2 reduces tumor growth, along with increased ferroptosis via inhibiting the expression of HIF-1/2α [54]. It is reported that the MIT-domain containing protein 1 (MITD1) is highly expressed in clear cell RCC, which suggests an unfavorable outcome in patients; moreover, knockdown of MITD1 promotes ferroptosis and impairs tumor migration and growth through the TAZ/SLC7A11 pathway [55]. Similarly, depletion of six-transmembrane epithelial antigen of prostate 3 (STEAP3) renders RCC cells more susceptible to erastin-induced ferroptosis via

activating the p53/xCT pathway, subsequently inhibits RCC progression [13]. Silencing of the suppressor of variegation 3–9 homolog 1 (SUV39H1) restrains clear cell RCC growth and progression but facilitates iron overload and lipid peroxidation, resulting in ferroptosis through enhancing the expression of the dipeptidyl-peptidase-4 [56]. These above studies imply that ferroptosis suppressors cause RCC cells escape from ferroptosis and promote tumor progression, thereby targeting these negative regulators of ferroptosis may provide novel strategies for RCC treatment.

It can be concluded that almost all reported oncogenic ferroptosis regulators are upregulated in RCC and promote tumor progression through restricting oxidative stress, iron overload, and lipid peroxidation. In addition, noncoding RNAs (ncRNAs) are increasingly regarded as important mediators modulating ferroptosis and are anticipated to be potential therapeutic targets in various tumors. Zhu et al. investigated the regulatory effects of miR-4735-3p on ferroptosis of RCC cells. In their study, a remarkable miR-4735-3p low expression was found in human RCC tissues and cell lines, and miR-4735-3p mimic inhibited RCC proliferation, which was along with elevated oxidative stress, lipid peroxidation, iron accumulation, and ferroptosis. Further mechanistic evaluation revealed that miR-4735-3p accelerated ferroptosis and tumor suppression in RCC by inactivating SLC40A1 [57]. In addition, it has been demonstrated that knockdown of lncRNA SLC16A1-AS1, which is upregulated in RCC, inhibits cell viability, proliferation, and migration RCC cells, as well as triggers ferroptosis through the miR-143-3p/SLC7A11 axis [58]. Therefore, ferroptosis-related ncRNAs participate in the progression of RCC. Further investigating the regulatory mechanism of ncRNAs on ferroptosis might provide a novel target in the treatment of RCC. Besides, SLC7A11 expression is linked to immune cell infiltration, including $CD8^{+}$ and myeloid dendritic cells, and is regulated by the ncRNA-mRNA axis in RCC [61]. It should be noted that ncRNAs-regulating ferroptosis in RCC progression is intricate due to its interaction with various pathological processes. The interplay between ncRNA-regulated ferroptosis and RCC pathogenesis should be further studied. Fig. 3 is an illustration of ferroptosis-related regulators and their respective mechanisms and functions.

3.7. Targeting ferroptosis in RCC treatment

As mentioned above, it is widely believed that ferroptosis play a regulatory role in RCC progression. So, targeting ferroptosis-related regulators would offer a promising therapeutic strategy for this disease.

Resistance to chemotherapy is a major hurdle in RCC treatment and causes poor prognosis. Recent studies have shown that ferroptosis inducers help to overcome sunitinib resistance in RCC. For example, curcumin combines with sunitinib suppresses the proliferation of sunitinib-resistant RCC cells by inducing ferroptosis via upregulating the ADAMTS18, a ferroptosis-related gene [62]. Similar to scenario observed in sunitinib-resistant RCC cells, artesunate exerts cytotoxic effects on RCC and represses cell proliferation and tumor growth through stimulating p53-dependent ferroptosis [63]. In addition, several natural compounds serve as ferroptosis inducers to promote RCC cell death. Luteolin, a natural flavonoid, triggers ferroptosis and reduces the survival of RCC cells, accompanied by excessive intracellular Fe^{2+}, mitochondrial ROS and abnormal depletion of GSH, which is attributed to the upregulation of HO-1 expression and activation of iron pool [64]. Likewise, icariside II reduces the proliferation, migration, and invasion in RCC cells by inducing ferroptosis via the miR-324-3p/GPX4 axis [65]. Furthermore, everolimus, an inhibitor of mTOR, facilitates the erastin and RSL3-induced ferroptosis in RCC cells, thus exerting a synergistical effect in ferroptosis-induced tumor growth suppression [9]. These findings indicate that activating ferroptosis in RCC inhibits tumor progression and chemoresistance. Table 2 is a detailed description of ferroptosis-inducing agents in RCC.

Thus, some drugs and natural compounds are capable of inducing ferroptosis and play an inhibitory role in the occurrence and

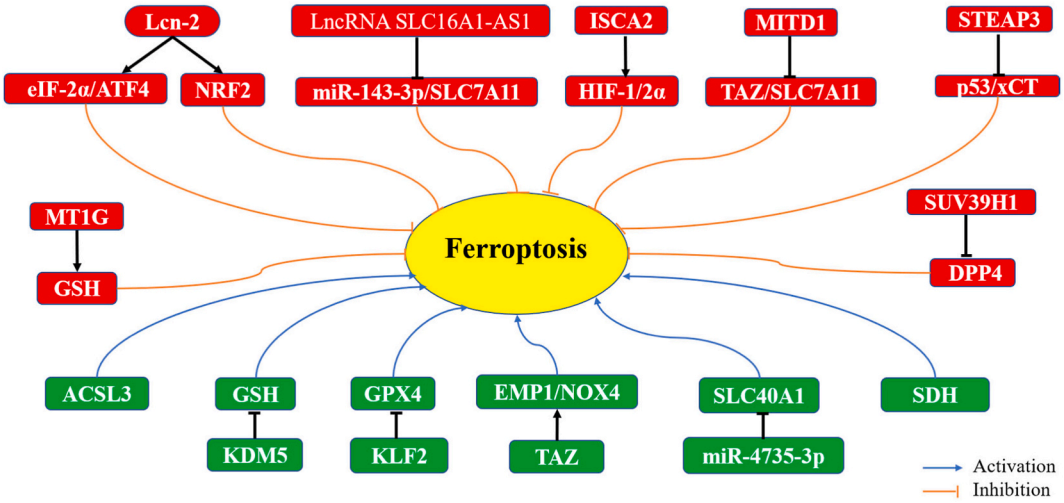

Fig. 3. Key pathways in regulation of ferroptosis in RCC. Some negative regulators (red) inhibit ferroptosis and promote RCC progression, while other positive regulators (green) promote ferroptosis and exert a tumor-suppressive role in RCC (see text). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Agents inducing ferroptosis in renal cell carcinoma.

Agent	Mechanism of Ferroptosis Induction	Experimental model	Study types	Ref.
Curcumin	Upregulation of ADAMTS18 level that promotes ferroptosis	A498 and 786O cell lines	In vitro	[62]
Artesunate	Activation of the p53-mediated ferroptosis	Caki1, 786O, KTCTL26 and A498 cell lines	In vitro	[63]
Luteolin	Upregulation of HO-1 expression that elevates Fe^{2+} and ROS levels and reduces GSH level	786O and OS-RC2 cell lines, OS-RC2 xenograft mouse model	In vitro, In vivo	[64]
Icariside II	Downregulation of GPX4 expression mediated by miR-324-3p	ACHN, A498, 786O and Caki1 cell lines; ACHN and Caki1 xenograft mouse model	In vitro, In vivo	[65]
Everolimus	Inhibition of mTOR pathway potentiates ferroptosis induced by erastin and RSL3	ACHN and Caki1 cell lines	In vitro	[12]

development of RCC. Further identification of the mechanisms by which various drugs or natural products regulate ferroptosis is crucial to develop targeted interventions in RCC. However, whether various targets acting on the ferroptosis exist in these drugs or natural products needs to be confirmed. Otherwise, the effect of most of the ferroptosis inducers has been studied in both cell experiments and animal models with no measurable side effects. The safety and efficacy of these drugs should be further evaluated in clinical settings for the treatment of RCC in the future.

3.8. *Ferroptosis-related prognostic markers in RCC*

Ferroptosis-related genes and proteins are believed to function as prognostic biomarkers in RCC. Acyl-CoA synthetase long-chain family member 4 (ACSL4), a mediator of ferroptosis, is identified to express at lower levels in clear cell RCC compared to normal tissues, which is related to an advanced tumor grade, nodal invasion, disease stage, and short overall survival in patients, suggesting ACSL4 may serve as a valuable biological marker for RCC [44]. By screening ferroptosis-associated genes that associated with prognosis of patients with RCC, Huang et al. identified farnesyl-diphosphate farnesyltransferase (FDFT1) as a ferroptosis marker, and

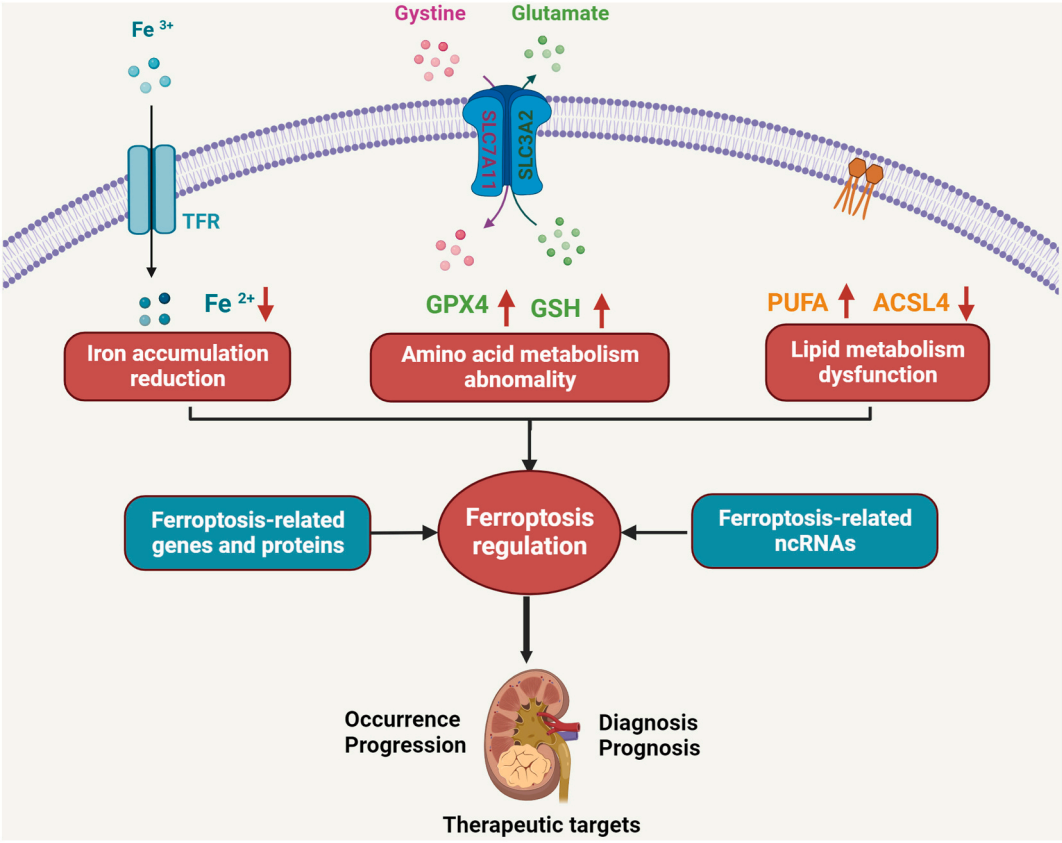

Fig. 4. The important role of ferroptosis in RCC. As a crucial form of RCC cell death, ferroptosis can suppress tumor progression. RCC cells are susceptible to iron overload and dysfunction in amino acid and lipid metabolism, which leads to abnormal ferroptosis and ultimately leads to tumor progression and unfavorable prognosis. Ferroptosis is also regulated by various genes, proteins and ncRNAs, which may provide potential clinical biomarkers and therapeutic targets for this disease.

found that overexpression of FDFT1 in the 786-O RCC cell line suppressed cell proliferation, migration, and invasion via the AKT signaling pathway, which also represented a novel therapeutic target for RCC [66]. In addition, Shi et al. established a ferroptotic genes-based signature for RCC prognosis, in which the glutaminase 2 gene was proved to be a suppressor of ferroptosis, since silencing this gene caused reduced glutathione levels but increased lipid peroxide levels [67]. Likewise, the decreased expression of short chain acyl-CoA dehydrogenase (ACADSB) is correlated with high tumor stage and grade and is regarded as an independent risk factor for the overall survival of patients with clear cell RCC, thus possessing diagnostic and prognostic potentials [33]. Consistently, several ferroptosis-related genes, such as CHAC1 and NCOA4, which are correlated with high-grade malignancy and advanced TNM stages, affect RCC progression and prognosis through shaping the oncogenic immune microenvironment [10,68]. Also, acyl-CoA Thioesterase 8 and 11 are believed to be promising biomarkers for diagnosis and prognosis of clear cell RCC, as they influence the development and progression of RCC via the regulation of oxidative phosphorylation and ferroptosis [69].

Since lncRNAs play crucial roles in regulating the progression of RCC by regulating ferroptosis, screening abnormal expressed lncRNAs may act as reliable biomarkers. Lai et al. prognostic model based on the ferroptosis-associated lncRNA signature may improve the survival prediction of RCC through making a classification in tumors [70]. These ferroptosis-related lncRNAs play an important role in the immune environment, immunotherapy response, and drug sensitivity of RCC, which helps to determine the individualized prognosis and treatment for RCC patients [71,72]. Dong et al. also established a ferroptosis-related lncRNA model that could accurately predict the prognosis of RCC, which is associated with oxygen metabolic processes and immune microenvironment [73]. Further analysis revealed that these prognostic models may regulate RCC immune function via modulating several key pathways, such as the P53 and tumor necrosis factor-mediated signaling pathway, which further affects stage, grade, and survival outcomes of RCC [74]. There are other prediction models showing ferroptosis-related lncRNAs related to T cell functions, macrophage polarization, immune checkpoints, and inflammation regulation in RCC [75,76]. These findings suggest that ferroptosis-related lncRNAs can be used as promising markers for the progression, prognosis, and personalized treatment of RCC.

These data suggest that the ferroptosis-related regulators and lncRNAs are dysregulated in RCC subtypes and could be employed as potential prognostic biomarkers to optimize patient monitoring and identify novel targets for more effective therapies. However, more attention should be paid to precise research, such as changes and functions of the regulators based on different tumor stages and types in larger samples.

4. Conclusions and future perspectives

This review emphasizes the importance of ferroptosis in progression, treatment, and prognosis of RCC. Ferroptosis induction are intimately related to metabolic disturbances in irons, amino acids, and lipids. RCC cells are predisposed to iron overload, and abnormalities in amino acid and lipid metabolism, which is associated with tumor progression and unfavorable prognosis in RCC patients, suggesting regulation of ferroptosis by targeting these metabolic signaling pathways may provide novel therapeutic strategies for this disease (Fig. 4). In fact, many ferroptosis-related genes or proteins are identified as modulators of ferroptosis affecting RCC proliferation, invasion, and metastasis. Positive regulators of ferroptosis inhibit RCC progression while negative ones exert the opposite effect, but the specific mechanisms by which these modulators regulate tumor development remain unclear. One possibility is that the paradoxical effects of ferroptosis regulators in RCC progression may depend on their different target genes in regulating specific cellular processes. Besides, the experimental findings are influenced by heterogeneity in cancer samples (cell lines, and tumor tissues from different individuals), insufficient sample size, varied testing methods, and other potential biases. Thus, future studies should take these factors into consideration for comprehensive and detailed investigations. Targeting these modulators to induce ferroptosis may be promising for RCC treatment. Most importantly, several ncRNAs are verified to influence RCC initiation and development by regulating ferroptosis, thus identifying ferroptosis-related ncRNAs and the regulatory role of ncRNAs in ferroptosis will shed light on the pathogenesis and therapies of this disease. Besides, some natural compounds that act as activators of ferroptosis have offered novel potential medicine for further development of promising strategies for RCC. Currently, there is no clinical trial of ferroptosis inducers in RCC, owing to the lack of insufficient research evidence on the functions and mechanisms of ferroptosis. For example, the effect of ferroptosis on RCC biological processes, such as DNA damage, angiogenesis, and tumor immunity, is elusive. In addition to ncRNAs, other upstream subjects and downstream targets of ferroptosis regulators remain unknown. Moreover, the biosafety and reliability of ferroptosis regulator-targeting therapeutics should be fully elucidated before clinical application. In this regard, further large-scale experiments should be carried out in the future to verify the role of ferroptosis in the progression and treatment of RCC. Furthermore, ferroptosis-related genes are expected to be employed as clinical markers for RCC diagnosis and prognosis, but the reproducibility, specificity, and sensitivity of these markers need to be further estimated before clinical application. Therefore, the establishment of ferroptosis-related biomarkers will contribute to better predictions of biological characteristics and optimal therapeutics for RCC.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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